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response filed the next business day, namely Monday, July 26, 2004, is considered timely. Accordingly, this Communication is being timely filed.

REMARKS

Claims 6, 8-10, 12-15, 29-32 and 34-37 are pending and under examination. No claim has been added, canceled or amended herein. Accordingly, claims 6, 8-10, 12-15, 29-32 and 34-37 are still pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the March 25, 2004 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods of treating or preventing thrombosis, and decreasing plasma fibrinogen. These methods comprise administering a tumor necrosis factor antagonist to a subject diagnosed as suffering from thrombosis.

This invention is based on applicants' *surprising discovery* that inhibiting the biological activity of TNF α reduces fibrinogen levels in a subject diagnosed as suffering from thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects diagnosed as suffering from thrombosis.

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Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 14, 15, 36 and 37 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states that the specification lacks deposit information for the cA2 antibody on which the instant method claims depend.

In response, applicants respectfully traverse the Examiner's rejection.

The Court of Appeals for the Federal Circuit has stated that:

No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988).

The Examiner states that the subject application, at page 8, lines 15-23, incorporates by reference information on cA2 in other U.S. patent applications not listed as priority documents. In particular, the subject application incorporates by reference information on cA2 described in U.S. Application No. 08/192,093, filed February 4, 1994 (now U.S. Patent No. 6,284,471), U.S. Application No. 08/192,102, filed February 4, 1994 (now U.S. Patent No. 5,656,272), U.S. Application No. 08/192,861, filed February 4, 1994 (now U.S.

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Patent No. 5,919,452), and U.S. Application No. 08/324,799, filed October 18, 1994 (now U.S. Patent No. 5,698,195).

Applicants point out that the instant specification teaches that monoclonal antibody cA2 consists of the antigen-binding variable region of murine monoclonal antibody A2 and the constant region of a human IgG1 κ immunoglobulin (see, e.g., page 12, lines 23-26).

Moreover, the instant specification provides ample guidance as to the structures of the cA2 chains. Specifically, at page 12, lines 12-22 of the specification, various U.S. patent applications, now issued U.S. patents, are referenced as teaching the nucleic acid and amino acid sequences of the cA2 light chain variable region and cA2 heavy chain variable region. For example, U.S. Application Nos. 08/192,093, filed February 4, 1994 (now U.S. Patent No. 6,284,471), 08/192,102, filed February 4, 1994 (now U.S. Patent No. 5,656,272), U.S. Application No. 08/192,861, filed February 4, 1994 (now U.S. Patent No. 5,919,452), and U.S. Application No. 08/324,799, filed October 18, 1994 (now U.S. Patent No. 5,698,195) disclose the nucleic acid and amino acid sequences of the cA2 light chain variable region (see Figure 16A of each of the above-referenced patents) and the cA2 heavy chain variable region (see Figure 16B of each of the above-referenced patents). The constant regions of a human IgG1 κ immunoglobulin are known and readily available in the art.

Furthermore, the referenced U.S. patent applications also provide significant description of the properties (e.g. glycosylation, epitopic specificity and affinity) of the

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chimeric anti-TNF α antibody cA2.

Applicants also point out that the monoclonal antibody cA2 is commercially available as Remicade (infliximab), a product developed and manufactured by Centocor, Inc., an assignee of U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272). See the Centocor, Inc.'s Remicade (infliximab) Products Webpage, http://www.centocor.com/cgi-in/site/products/prod_remicade.cgi (June 22, 2004) (a printout of which is attached hereto as **EXHIBIT A**). See also the October 28, 1999 Pharmacological Review for Remicade (infliximab) from the U.S. Food and Drug Administration's Center For Drug Evaluation And Research, <http://www.fda.gov/cder/biologics/review/inflcen111099r2.pdf> (June 21, 2004) (a printout of which is attached hereto as **EXHIBIT B**), and the Label and Approval History for Remicade (infliximab) from the U.S. Food and Drug Administration's Center for Evaluation And Research, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (June 21, 2004) (a copy of which is attached hereto as **EXHIBIT C**).

Examiner also states that information on cA2 described in other patent applications is no guarantee that the cA2 antibody will be publicly available for the life of the instant patent.

In response, according to M.P.E.P. §2404.02, "[u]nless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent, current availability would satisfy the requirement."

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Applicants note that (1) the Examiner has not provided any basis for reasonably believing that the biological material will cease to be available during the enforceable life of the patent, and (2) the monoclonal antibody cA2 is commercially available as Remicade (infliximab), a product developed and manufactured by Centocor, Inc., an assignee of U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272).

With the information provided in the referenced U.S. patent application mentioned above and the commercial availability of monoclonal antibody cA2, one skilled in the art would be able to readily obtain the monoclonal antibody cA2 for use in the claimed invention without undue experimentation. Thus, the monoclonal antibody cA2 is enabled by the present specification, in view of the incorporation by reference of the referenced applications, as well as the current availability of cA2 as Remicade (infliximab), and a deposit is not required.

In view of the above remarks, applicants maintain that claims 14, 15, 36 and 37 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §112, Second Paragraph -
Indefiniteness

On page 2, paragraph 3 of the March 25, 2004 Final Office Action, the Examiner indicated that the rejection of claims 14, 15, 36 and 37 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention is withdrawn in light of applicants

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amendments.

Applicants note, however, that the above statement is immediately followed by the sentence: "access (sic) number would overcome this rejection." Applicants view this sentence as an inadvertent error. However, should the Examiner continue to reject claims 14, 15, 36 and 37 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention, applicants respectfully traverse the Examiner's rejection.

As mentioned above, the instant specification teaches that monoclonal antibody cA2 consists of the antigen-binding variable region of murine monoclonal antibody A2 and the constant region of a human IgG1 κ immunoglobulin (see, e.g., page 12, lines 23-26). The instant specification provides ample guidance as to the structures of the cA2 chains. Specifically, at page 12, lines 12-22 of the specification, various U.S. patent applications, now issued U.S. patents, are referenced as teaching the nucleic acid and amino acid sequences of the cA2 light chain variable region and cA2 heavy chain variable region as discussed above. Moreover, the referenced U.S. patent applications also provide significant description of the properties (e.g. glycosylation, epitopic specificity and affinity) of the chimeric anti-TNF α antibody cA2.

The referenced patent applications provide significant description of the properties and methods for producing chimeric monoclonal antibody cA2, thereby clearly establishing

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that the characteristics of cA2 are known and that the term clearly defines an antibody whose features are well defined. Applicants also note that employing a laboratory designation in a claim is not *per se* impermissible.

In view of the above remarks, applicants maintain that claims 14, 15, 36 and 37 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §103(a) - Obviousness

The Examiner rejected claims 6, 8, 29 and 30 under 35 U.S.C. §103(a) as allegedly unpatentable over Wakefield, et al. (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pages 258-268), in view of Arbustini, et al. (American Journal of Cardiology, 1991, Vol. 68, pages 36B-50B), as evidenced by the abstract of Riipi, et al. (Infection and Immunity, 1990, Vol. 58, pages 2750-2754).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks in the November 21, 2003 Communication made in connection with the non-obviousness of the claimed subject matter, and make the following additional remarks to underscore their position.

Claims 6, 8, 29 and 30 provide methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject diagnosed as

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suffering from thrombosis.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every limitation of the claims. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, to support a *prima facie* case of obviousness, the teachings of Wakefield, et al., Arbustini, et al. and Riipi, et al., at the time of the invention, would have to teach every limitation set forth in the claimed invention. Moreover, these references would also have to provide a reasonable expectation of success.

Wakefield, et al., Arbustini, et al. and Riipi, et al. fail to do this.

Wakefield, et al. teaches that anti-TNF antibodies partially reduce vein wall neutrophil extravasation, and thus partially inhibit the vein wall inflammatory response which occurs as a result of venous thrombosis. Wakefield, et al. suggests that a decrease in the vein wall inflammatory response may result in a decline in the manifestations of chronic venous insufficiency, a syndrome which occurs after venous thrombosis. However, Wakefield, et al. does not teach or suggest the treatment or prevention of thrombosis, or decreasing plasma fibrinogen, itself. It also does not teach

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or suggest methods for treating a subject diagnosed as suffering from thrombosis.

Arbustini, et al. teaches that TNF has been immunohistochemically detected in smooth muscle cells, endothelial cells and macrophages of human femoral, coronary and carotid atherosclerotic arteries, and therefore, may play a role in the evolution of disease (i.e., atherosclerosis). However, Arbustini, et al. also teaches that TNF α was found in lipid-rich plaques either with or without thrombus. Furthermore, Arbustini, et al. states that "[i]nterestingly, like inflammatory infiltrates and TNF α , IL-2 is present in plaques with large amounts of pultaceous core not strictly related to thrombosis but rather to the plaque composition." Arbustini, et al., page 49B. Thus, similar to Wakefield, et al., Arbustini, et al. does not teach or suggest methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, itself, let alone teach methods for treating a subject diagnosed as suffering from thrombosis.

The abstract of Riipi, et al. also does not cure the deficiencies of Wakefield, et al. and Arbustini, et al. Riipi, et al. teaches that pre-administration of anti-mouse-TNF α polyclonal antibodies in mice results in the inhibition of the increase of plasma fibrinogen that occurs upon challenge with *Candida albicans* or mouse TNF α . Riipi, et al. does not teach or suggest methods of treating or preventing thrombosis. In fact, nowhere does Riipi, et al. even mention the term "thrombosis." Furthermore, Riipi, et al. does not teach or suggest methods of decreasing plasma fibrinogen in a subject diagnosed as suffering from thrombosis.

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Thus, in light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every limitation of the claims, or present a motive to combine or a reasonable expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 29 and 30 over Wakefield, et al., Arbustini, et al. and Riipi, et al.

The Examiner also rejected claims 6, 8-10, 12-15, 29-32 and 34-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Wakefield, et al., in view of Arbustini, et al. and the abstract of Riipi, et al., and further in view of Le, et al. (U.S. Patent No. 5,656,272).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks in the November 21, 2003 Communication made in connection with the non-obviousness of the claimed subject matter, and make the following additional remarks to underscore their position.

Again, claims 6, 8-10, 12-15, 29-32 and 34-37 provide methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject *diagnosed as suffering from thrombosis*. In one embodiment of the invention, the TNF antagonist is an anti-TNF

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antibody. In another, the antibody is the chimeric monoclonal anti-TNF antibody cA2.

To support a *prima facie* case of obviousness, Wakefield, et al., Arbustini, et al. and Riipi, et al., combined with Le, et al., would have to teach every limitation set forth in the claimed invention. Moreover, these references, when combined, would have to provide a reasonable expectation of success.

Wakefield, et al., Arbustini, et al. and Riipi, et al., combined with Le, et al., do not do this.

Wakefield, et al., Arbustini, et al. and Riipi, et al. are discussed above. Again, these references combined do not teach or suggest methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject *diagnosed as suffering from thrombosis*.

Le, et al. fails to cure the deficiencies of Wakefield, et al., Arbustini, et al. and Riipi, et al. Instead, Le, et al. teaches methods of treating a large number of TNF α -mediated pathologies and conditions generally with anti-TNF α antibodies, including cA2.

Le, et al. does not teach or suggest the treatment or prevention of thrombosis, or of increased plasma fibrinogen, in a subject diagnosed as suffering therefrom. Le, et al., does not include thrombosis or plasma fibrinogen in their exhaustive list of TNF α -mediated pathologies and conditions,

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nor does it even mention the terms "thrombosis" or "plasma fibrinogen." See, e.g., Le et al., col. 34, line 7 to col. 35, line 5. Therefore, Le, et al., in combination with the other cited references, does not provide an impetus for using this antibody method in connection with a method of the type claimed.

Thus, in light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every limitation of the claims, or present a motive to combine or a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8-10, 12-15, 29-32 and 34-37 over Wakefield, et al., in view of Arbustini, et al. and the abstract of Riipi, et al., and further in view of Le, et al.

The Examiner also rejected claims 6, 8, 29 and 30 under 35 U.S.C. §103(a) as allegedly unpatentable over Wakefield, et al., in view of Arbustini, et al., as evidenced by the abstract of Riipi, et al., and further in view of Esser (WO 92/09203).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks in the November 21, 2003 Communication made in connection with the non-obviousness of the claimed subject matter, and make the following additional remarks to underscore their position:

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Again, claims 6, 8, 29 and 30 provide methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject *diagnosed as suffering from thrombosis*.

Wakefield, et al., Arbustini, et al. and Riipi, et al. are discussed above. Again, these references combined do not teach or suggest methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject diagnosed as suffering from thrombosis.

Esser fails to cure the deficiencies of Wakefield, et al., Arbustini, et al. and Riipi, et al. Esser teaches essentially what Le, et al. teach, i.e., general methods of treating various TNF-mediated diseases with TNF inhibitors.

Esser does not teach or suggest the treatment or prevention of thrombosis, or of increased plasma fibrinogen, in a subject diagnosed as suffering therefrom. Although Esser theorizes that since TNF has pro-inflammatory activities, its early production, i.e., during the initial stages of an inflammatory event, make it a likely mediator of tissue injury in disorders such as myocardial infarction and stroke, Esser does not recite the terms "thrombosis" or "plasma fibrinogen" as related to TNF α -mediated diseases, nor does it even mention methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, in a subject diagnosed as suffering from thrombosis.

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Thus, in light of these teachings and their shortcomings, the Examiner has failed to show that the cited references combined teach or suggest every limitation of the claims, or present a motive to combine or a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 29 and 30 over Wakefield, et al., in view of Arbustini, et al., as evidenced by the abstract of Riipi, et al., and further in view of Esser.

In view of the above remarks, applicants maintain that claims 6, 8-10, 12-15, 29-32 and 34-37 satisfy the requirements of 35 U.S.C. §103(a).

Provisional Obviousness-Type Double Patenting

The Examiner states that claims 6, 8-10, 12-15, 29-32 and 34-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of co-pending Application No. 09/598,079, claims 1-23 of co-pending Application No. 09/754,004, claims 32-54 of co-pending Application No. 09/921,937 and claims 1-20 of co-pending Application No. 10/252,489, all in view of Wakefield, et al. and Arbustini, et al., as evidenced by the abstract of Riipi, et al.

In response, applicants note that, should this rejection become non-provisional, applicants will either traverse the rejection and set forth their grounds for doing so, or will file a terminal disclaimer, whichever action is deemed

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appropriate.

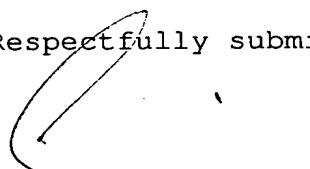
Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

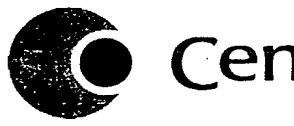
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the \$110.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,


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Remicade® (infliximab) is a chimeric monoclonal antibody that binds to tumor necrosis factor alpha (TNF- α), which is believed to be a central causative factor in the inflammatory process in humans.¹

On August 24, 1998, the FDA approved Remicade for the treatment of moderately to severely active Crohn's disease for the reduction of signs and symptoms, in patients who have had an inadequate response to conventional therapy, and for the treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s). It is the first and only FDA-approved product indicated for this serious gastrointestinal disorder.²

On November 10, 1999, FDA approval was granted for the use of Remicade in combination with methotrexate for the reduction in signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate alone. Remicade is the first monoclonal antibody to reduce the signs and symptoms of this crippling disease.

On December 29, 2000, the FDA granted Centocor approval to market Remicade, in combination with methotrexate, for inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

The approval of the most recent indication - inhibiting the progression of structural damage - was based on 54-week data from the two-year ATTRACT trial (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant

Therapy) involving 428 patients at 34 centers in North America and Europe. Patients treated with Remicade, in combination with methotrexate, were compared to those patients treated with methotrexate plus a placebo.³

In the ATTRACT trial, progression of joint damage was measured radiographically using the van der Heijde modified Sharp scoring system, which evaluates changes in joint-space narrowing and bone erosions. Among all Remicade treatment groups, the overall median change from baseline for total radiographic scores (erosions and joint-space narrowing) was 0.0 among patients treated with the combination of Remicade plus methotrexate (n=285) compared to a median change of 4.0 for patients treated with methotrexate alone (n=64). A total of 53 percent of Remicade patients demonstrated no deterioration in their total van der Heijde modified Sharp score at 54 weeks. The patients treated with methotrexate plus placebo demonstrated progression comparable to that previously reported for patients with established rheumatoid arthritis treated with methotrexate.

Many people with heart failure should not take Remicade; so, prior to treatment patients should discuss any heart condition with their doctor. Patients should tell their doctor right away if they develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of their feet).

There are reports of serious infections, including tuberculosis (TB) and sepsis. Some of these infections have been fatal. Patients should tell their doctor if they have had recent or past exposure to people with TB. Their doctor will evaluate them for TB and perform a skin test. If a patient has latent (inactive) TB, his or her doctor should begin TB treatment before starting Remicade. If a patient is prone to or has a history of infections, currently has one, or develops one while taking Remicade, he or she should tell his or her doctor right away. Patients should also tell their doctor if they have lived in a region where histoplasmosis is common or if they have or have had a disease that affects the nervous system, or if they experience any numbness, tingling, or visual disturbances.

There are also reports of serious infusion reactions with hives, difficulty breathing, and low blood pressure. In clinical studies, some people experienced the following common side effects: upper respiratory infections, headache, nausea, cough, sinusitis or mild reactions to the infusion such as rash or itchy skin. Please read important information about Remicade, including full prescribing information, at www.Remicade.com.

Full Prescribing Information

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Remicade in Crohn's Disease

- Remicade is a chimeric monoclonal antibody that binds to tumor necrosis factor alpha (TNF- α), which is believed to be a central causative factor in the inflammatory process in humans.¹
- Remicade is the first and only FDA-approved product indicated for the treatment of Crohn's disease.²
- On August 24, 1998, the U.S. Food and Drug Administration (FDA) approved Remicade for the reduction in signs and symptoms of Crohn's disease in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, and for the treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s). The safety and efficacy of therapy continued beyond the recommended dosage have not been established.³
- Since the first marketing approval in the United States in 1998, approximately 230,000 patients have been treated with Remicade worldwide.³
- Remicade is appropriate for patients who are unresponsive to conventional therapy, including patients dependent on, intolerant of, or refractory to steroids, and those with single or multiple draining fistula(s).³
- Many people with heart failure should not take Remicade; so, prior to treatment patients should discuss any heart condition with their doctor. Patients should tell their doctor right away if they develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of their feet).

There are reports of serious infections, including tuberculosis (TB) and sepsis. Some of these infections have been fatal. Patients should tell their doctor if they have had recent or past exposure to people with TB. Their doctor will evaluate them for TB and perform a skin test. If a patient has latent (inactive) TB, his or her doctor should begin TB treatment before starting Remicade. If a patient is prone to or has a history of infections, currently has one, or develops one while taking Remicade, he or she should tell his or her doctor right away. Patients should also tell their doctor if they have lived in a region where histoplasmosis is common or if they have or have had a disease that affects the nervous system, or if they experience any numbness, tingling, or visual disturbances.

There are also reports of serious infusion reactions with hives, difficulty breathing, and low blood pressure. In clinical studies, some people experienced the following common side effects: upper respiratory infections, headache, nausea, cough, sinusitis or mild reactions to the infusion such as rash or itchy skin. Please read important information about Remicade, including full prescribing information, at www.Remicade.com.

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Remicade in Rheumatoid Arthritis

- Remicade is a chimeric monoclonal antibody that binds to TNF- α , which is believed to be a central causative factor in the inflammatory process in humans.¹
- On December 29, 2000, the FDA granted Centocor approval to market Remicade, in combination with methotrexate, for inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate. Remicade, in combination with methotrexate, was approved in November 1999 for the treatment of signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate alone.³
- Remicade was specifically designed to target a single substance in the body called TNF- α . TNF- α is a key regulatory of inflammation in RA. Inflammation, in turn, produces the symptoms of RA, including joint stiffness and pain. By inactivating TNF- α , the inflammatory process is significantly diminished from the start.^{1,4}
- Remicade targets TNF- α with high specificity, affinity and avidity. High affinity and avidity of Remicade result in a tight complex, neutralizing TNF- α activity. Remicade binds only to TNF- α . Remicade does not bind to lymphotoxin- α (TNF- β), a related cytokine. The clinical relevance of this has not been established.^{1,3,4}
- Remicade is the first monoclonal antibody to reduce the signs and symptoms of rheumatoid arthritis.⁵
- Remicade is the first and only drug approved by the FDA to improve physical function and inhibit the progression of joint damage, in addition to providing relief for the pain and stiffness of rheumatoid arthritis. Remicade is used in combination with methotrexate when methotrexate alone has not worked well.
- Remicade is used with methotrexate when methotrexate alone hasn't worked well. Many people with heart failure should not take Remicade; so, prior to treatment patients should discuss any heart condition with their doctor. Patients should tell their doctor right away if they develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of their feet).

There are reports of serious infections, including tuberculosis (TB) and sepsis. Some of these infections have been fatal. Patients should tell their doctor if they have had recent or past exposure to people with TB. Their doctor will evaluate them for TB and perform a skin test. If a patient has latent (inactive) TB, his or her doctor should begin TB treatment before starting Remicade. If a patient is prone to or has a history of infections, currently has one, or develops one while taking Remicade, he or she should tell his or her doctor right away. Patients should also tell their doctor if they have lived in a region where histoplasmosis is common or if they have or have had a disease that affects the nervous system, or if they experience any numbness, tingling, or visual disturbances.

There are also reports of serious infusion reactions with hives, difficulty breathing, and low blood pressure. In clinical studies, some people experienced the following common side effects: upper respiratory infections, headache, nausea, cough, sinusitis or mild reactions to the infusion such as rash or itchy skin. Please read important information about Remicade, including full prescribing information, at www.Remicade.com.

Full Prescribing Information

To read the PDF file you will need Adobe® Acrobat® Reader. [Click here to download it.](#)

References: **1.** Knight DM, Trinh H, Siegel S, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF Antibody. *Molecular Immunology*. 1993;30(16):1443-1453. **2.** HHS News, US Department of Health & Human Services; Food and Drug Administration, 8/24/98:P98-23. **3.** Data on file, Centocor, Inc. **4.** Scallan BJ, Moore MA, Trinh H, Knight DM, Ghrayeb J. Chimeric anti-TNF-a monoclonal antibody cA2 binds recombinant trans-membrane TNF-a and activates immune effect functions. *Cytokine*. 1995;7:251-259. **5.** Elliot MJ, Maini RM, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor a. *Arthritis Rheum*. 1993;36:1681-1690.

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Memorandum:

DRAFT

To File: BLA 99-0128
From: Lauren E. Black, Ph.D., *L.E.B.* Reviewing Pharmacologist
Through: M. David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch
Through: Karen Weiss, M.D., Director, Division of Clinical Trials Design and Analysis
Subject: Pharmacology Review of the infliximab BLA
Product: Remicade®, Infliximab (cA2), chimeric (human/murine) IgG1 for use in Rheumatoid Arthritis
Sponsor: Centocor, Inc.
Date: 10/28/99

BACKGROUND: Infliximab has very limited crossreactivity and binds only to human and chimpanzee TNF α . The sponsor has produced a highly analogous mouse-rat chimeric antibody directed at mouse TNF α which is designated cV1q by replacing the rat heavy and light chain constant domains with those from a mouse IgG2a antibody. Prior to initiating multiple dose toxicity studies (i.e. fertility and general reproduction and 6-month chronic studies) with cV1q in mice, a pharmacokinetic and tolerance study was conducted to assure that at least 3 months of once weekly intravenous dosing would be tolerated and that high cV1q serum levels could be maintained (see review below). Dosing was consistent with pharmacologically active doses and schedules utilized in murine activity models. Development of mouse anti-chimeric antibodies (MACA) were evaluated; cV1q proved to be sufficiently nonimmunogenic in mice such that long term studies are feasible and pharmacologically relevant to assessing risk of the human drug.

INTRODUCTION: This is the — BLA for infliximab. There are two toxicology issues new to this file. The first issue is the chronic dosing regimen proposed for the RA indication, necessitating the conduct of a new chronic toxicology study. This decision is in keeping with two ICH documents, M3 and S6, pertaining to clinical risk assessment of drugs and biologic therapies. cV1q is currently being dosed in mice for 6 months. While the starting date for the chronic toxicology study was originally intended to provide draft toxicology data to the BLA during its review period at FDA, the study start was delayed due to a production setback. Since cV1q is analogous and non-identical to the human product, we have agreed with the sponsor that the study could be completed and reported post approval. Study results are expected for submission to FDA in the year 2000. Based on the broader clinical population treated with infliximab, it was desirable from a public health perspective to evaluate the effects of infliximab on additional reproductive endpoints. The sponsor evaluated cV1q in mice in a study of male and female fertility and general reproductive performance (see review below).

REGULATORY CONCLUSIONS: These studies (completed and in progress) are adequate to support the proposed labeling for the current clinical indication. No changes to the sponsor's proposed wording are required. See Dr. Matthew's review regarding clinical issues.

CONCLUSIONS: Based on review of the pharmacology and toxicology data, the safety of infliximab is adequately supported, and no objection is offered to approving this licensing application. The review is provided as an attachment to this cover sheet.

REVIEWER: *Lauren E. Black*

Lauren E. Black, Ph.D., Reviewing Pharmacologist, DCTDA, CBER

CONCURRENCE: *Martin D. Green*

Martin David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch, DCTDA, CBER

cc: M.D. Green, Ph.D., L. Paserchia, M.D., L.E. Black, Ph.D., HFM-579

B. Matthews, M.D., HFM-582; K. Brorson, Ph.D., HFM-561; M. Noska, HFM-588

ATTACHMENT

ATTACHMENT

PHARMACOLOGY AND TOXICOLOGY SYNOPSIS BLA (98-0012) FOR CROHN'S DISEASE:

Tissue Crossreactivity: Chimeric A2 (cA2) showed no unexpected reactivity (or cross-reactivity) in *in vitro* human tissue cross-reactivity assessment, nor mutagenicity, local intolerance, reproductive, or other systemic toxicities that would preclude its use in Crohn's Disease patients.

Pharmacology: The following pharmacologic properties can be attributed to cA2:

- cA2 binds to TNF α homotrimer with high affinity ($K_a = 10^{10} M^{-1}$); it specifically neutralizes TNF α and does not neutralize lymphotoxin.
- cA2 also binds to both the monomeric subunits of TNF α and transmembrane TNF α ; after cA2 binds to cells expressing transmembrane TNF α they can be lysed by the addition of complement or effector cells.
- The stable complex formed between TNF α and cA2 is responsible for blocking TNF α activity.

Safety Studies in Chimpanzees with cA2: The chimpanzee is the only species other than humans whose TNF α binds to cA2, therefore safety studies in this species are considered the only preclinical studies that can provide direct safety information on cA2 administration to humans. However, due to animal use restrictions on this endangered species, these animals may not be necropsied to provide histopathology data, and therefore study outcomes are limited to clinically observable signs as well as results from noninvasive testing (such as clinical chemistry and hematology assessments). Following some problems attributable to high doses of ketamine anesthetic required for animal handling, the studies with cA2 in chimpanzees showed that cA2 was well tolerated at doses up to 30 mg/kg/day for at least 3 consecutive days and at doses up to 15 mg/kg/day for at least 5 days. No cA2-related signs of toxicity, including abnormal hepatic or hematologic effects, were observed during these chimpanzee studies. cA2 has a long serum half-life (6 days in chimpanzees) and predictable pharmacokinetics.

Mouse Studies with Analogous Antibody: Doses of cV1q, an analogous anti-mouse TNF α monoclonal antibody which were active in a mouse model of disease, when given to pregnant mice during organogenesis, caused no embryofetal toxicities. These studies were necessitated due to the absence of crossreactivity of cA2 in species other than chimpanzees.

NEW STUDIES.

CHRONIC PHARMACOKINETICS:

12-Week Intravenous Dose Pharmacokinetic and Tolerance Study of cV1q Anti-Mouse TNF α Antibody in CD-1® Mice (Centocor Study P-098-018)

The purpose of this study was to evaluate the pharmacokinetics and potential toxicity of cV1q in mice when administered intravenously once weekly for 12 consecutive weeks. Based on the results of this study, the feasibility of conducting multiple dosing toxicity and/or pharmacology studies with cV1q was determined.

Ten male CD-1® mice were obtained from [REDACTED]. The mice were assigned to two treatment groups (5 mice/group). cV1q (Lots [REDACTED] and [REDACTED] 5 mg/mL) was administered at a dose of 10 or 40 mg/kg at a dose volume of 10 mL/kg. Chimeric V1q was administered intravenously (bolus dose) into the caudal vein once weekly for 12 consecutive weeks. Clinical signs were recorded daily. Body weights were recorded predose and just prior to each weekly dose. Serum samples were collected from all study mice one day prior to weekly doses 1, 2, 4, 8, 10 and 12, and at week 13 for determination of serum cV1q concentration. Alanine transaminase (ALT) was evaluated in serum samples collected at study week 13. Other serum chemistry parameters were not evaluated because of the limited sera available for testing. All study mice were euthanized and submitted to necropsy at 13 weeks (7 days after the 12th dose). Brain, adrenal gland, lung, liver, spleen, kidney, urinary bladder, heart, mesenteric lymph node, colon and small intestine were collected and fixed in 10% buffered formalin. Histopathologic examination was performed by light microscopy on hematoxylin/eosin stained tissues/organs.

No mortality or signs of toxicity were observed during the study in CD-1® mice administered 12 weekly intravenous doses (10 or 40 mg/kg/dose) of cV1q. No changes considered to be cV1q treatment-related were observed for body weight, ALT or histopathologic evaluations. Serum cV1q concentration analyses revealed that weekly intravenous doses of cV1q at 10 and 40 produced high serum cV1q concentrations. Serum cV1q concentrations for the 10 mg/kg dose group reached a steady state after 9 weekly doses (> 200 mg/mL). Serum cV1q concentrations for the 40 mg/kg dose group reached concentrations of approximately 800 mg/mL after 7 doses, but by the end of the study the serum concentrations were lower (> 400-500 mg/mL).

Thus, cV1q was well tolerated in CD-1® mice following 12 weekly intravenous doses of 10 or 40 mg/kg. Serum cV1q concentration analyses revealed that high serum concentrations of cV1q were achieved and maintained during the study.

REPRODUCTIVE TOXICITY

Intravenous Fertility and General Reproduction Toxicity Study of cV1q Anti-Mouse TNF α Antibody in CD-1® Mice (Centocor Study T-098-003)

The purpose of this study was to evaluate the potential toxic effects of cV1q on fertility and general reproduction in male and female mice. This study was designed to evaluate ICH Harmonized Tripartite Guideline stages A and B of the reproductive process. This included detection of potential effects on the estrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryos of female mice and permit detection of functional effects (e.g., effects on libido or epididymal sperm maturation) that may not be detected by histological examinations of male mouse reproductive organs.

Seventy-five male and 75 female CD-1® mice, obtained from (_____) were randomly assigned to three dose groups (25/sex/dose group). Prior to randomization the females were evaluated for evidence of normal estrous cycling. The three dose groups were administered intravenously (bolus dose) into the caudal vein with either control vehicle (1X Dulbecco's Phosphate Buffered Saline) or cV1q (Lots _____ and _____ 0.5 mg/mL and 2.0 mg/mL). cV1q was administered at dosages of 10 and 40 mg/kg/dose. Both cV1q and control vehicle were administered at a dose volume of 20 mL/kg.

Male mice were administered cV1q or control vehicle once weekly beginning 56 days (8 weeks) before cohabitation and continuing through cohabitation (2 weeks) and the week before sacrifice. Female mice were administered cV1q or control vehicle once weekly beginning 2 weeks before cohabitation (maximum of 14 days) and on day 0 and day 7 of gestation. All mice were observed once daily for clinical signs, except on dose days, when observations were recorded before injection and for approximately 60 minutes after injection. Body weights were measured weekly. In addition, the female mice were weighed daily during the gestation period. Blood samples were collected from all surviving male and female mice just prior to necropsy for cV1q serum concentration analyses. Female mice were Caesarian-sectioned on day 11 of gestation and the thoracic, abdominal and pelvic viscera grossly examined and gross lesions collected in neutral buffered formalin. The number of corpora lutea in each ovary was recorded. The uterus was excised and examined for pregnancy, number and distribution of implantations and viable and nonviable embryos. The ovaries were collected in neutral buffered formalin for possible future evaluation. Male mice were sacrificed after completion of the cohabitation period and the thoracic, abdominal and pelvic viscera were grossly examined and gross lesions collected in neutral buffered formalin.

The following male organs were individually weighed and collected in neutral buffered formalin (the testes were fixed in Bouin's solution for 48 to 96 hours before being placed in formalin): right testis, left testis, left epididymis, right epididymis, seminal vesicles and prostate. Sperm concentration and motility were evaluated.

Several male and female animals died during the study. Male mortalities included one mouse in the 0 (vehicle control) and 10 mg/kg dosage groups and two mice in the 40 mg/kg dosage group. Female mortalities included four mice in the 10 mg/kg dosage group and three mice in the 40 mg/kg dosage group. No gross findings related to cV1q treatment were observed at necropsy and the exact causes of

death were not determined. However, it is possible that the deaths for the cV1q-treated animals were related to hypersensitivity reactions to multiple cV1q doses since most of the deaths occurred on the day of dosing following 3 to 6 weekly doses. No signs of toxicity or body weight changes considered cV1q-related were observed during the study in either male or female treated mice. Estrous cycling was unaffected by cV1q treatment. All mating and fertility parameters [fertility and pregnancy indices (number of pregnancies per number of mice in cohabitation and mice that mated, respectively), number of days to inseminate, number of mice that mated and number of mice with confirmed mating dates during the first and second week of cohabitation] were unaffected by cV1q treatment. Only one mouse failed to have a confirmed date of mating. Pregnancy occurred in 23 (92%), 21 (91%) and 19 (76%) of the female mice in the 0 (vehicle control), 10 and 40 mg/kg dosage groups, respectively. The slightly lowered pregnancy rate in the 40 mg/kg dosage group was not considered related to cV1q treatment, because the pregnancy rate was only slightly lower than the historical control range (83-100%) for the Test Facility _____) and there was no effect on fertility parameters evaluated at Caesarean-sectioning.

No litter parameters were affected by cV1q. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weights, percent resorbed conceptuses, and percent live male fetuses were comparable among the cV1q and vehicle control treatment groups and did not significantly differ. No dam had a litter consisting of only resorbed conceptuses, and there were no dead fetuses. No cV1q-related necropsy findings were observed in male or female animals. No organ weight changes considered cV1q-related were observed in the male animals. The number of motile sperm, motile percent, nonmotile and total and sperm count were unaffected by cV1q treatment. Serum cV1q concentration analyses from samples collected just prior to necropsy showed that weekly doses of cV1q at 10 and 40 mg/kg produced significant cV1q serum concentrations in both male and female animals, which verified cV1q exposure during the study.

Thus, cV1q at weekly dosages of 10 and 40 mg/kg in male and female CD-1® mice produced no toxic effects on fertility and general reproduction in male and female mice. The new wording for the Remicade label as currently proposed by the sponsor (10/28/99) is as follows: "No impairment of fertility was observed in a fertility and general reproduction toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFa." This is an adequate description of the results.

DESIGN FOR THE CHRONIC INTRAVENOUS DOSE TOXICITY STUDY (IN PROGRESS)

1) 6-Month Chronic Toxicity Study of cV1q muG2a Anti-Mouse TNFa Antibody in CD-1® Mice (Centocor Study T-098-004) The purpose of this study is to evaluate the potential toxicity of cV1q, anti-mouse TNFa monoclonal antibody, in CD-1® mice when administered intravenously once weekly for six months. In this 6-month chronic toxicity study, 240 CD-1® mice (120 male and 120 female) will be obtained from _____ and assigned to dose groups shown in Table 3.

Table 1 Study design for study T-098-004

Dose Group	Dose	Number of Mice Submitted to Necropsy									
		Initiated		3 Months		6 Months		Recovery			
		M	F	M	F	M	F	M	F		
Control	0	40	40	10	10	20	20	10	10		
cV1q	10	40	40	10	10	20	20	10	10		
cV1q	40	40	40	10	10	20	20	10	10		

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Label and Approval History

Drug Name(s) REMICADE (Brand Name Drug)

FDA Application No. (BLA) 103772

Active Ingredient(s) INFliximab

Company CENTOCOR INC

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Label Information

What information does a label include?

Note: Not all labels are available in electronic format from FDA.

The latest approved label (approved 09/03/2003) is *not available* on this site for REMICADE, BLA no. 103772

[View the label approved on 06/28/2002](#)

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Action dates can only be verified from 1984 to the present.

Action Date	Supplement Number	Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
09/03/2003	5056	Supplement	<u>Letter</u>	Label is not available on this site.
09/03/2003	5020	Supplement	<u>Letter</u>	Label is not available on this site.
04/01/2003	5032	Supplement	<u>Letter</u>	Label is not available on this site.
06/28/2002	5012	Supplement	<u>Label</u> <u>Letter</u>	

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Applicants: Michael J. Elliott, et al.

Serial No. : 08/602,272

Filed: February 16, 1996

Exhibit C

02/27/2002	5004	Supplement	<u>Label</u>  <u>Letter</u> 	
12/29/2000	1007	Supplement	<u>Label</u>  <u>Letter</u> 	
11/10/1999	1004	Supplement	<u>Label</u>  <u>Letter</u>  <u>Review</u> 	

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